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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,044	04/07/2006	Anne Angelillo-Scherrer	50304/009003	1775

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

NOTIFICATION DATE	DELIVERY MODE
11/25/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	10/595,044	ANGELILLO-SCHERRER ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,28-30 and 32* is/are pending in the application.

4a) Of the above claim(s) *28 and 29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,30 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/8/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08 October 2009 has been entered.

Status of Application, Amendments and/or Claims

The amendment and Applicant's arguments, filed 11 August 2009, have been entered in full. Claims 28 and 29 are withdrawn. Claims 1-20, 22-27 and 31 are canceled. Claim 21 is amended. Claims 21, 30 and 32 are under examination.

Information Disclosure Statement

The information disclosure statement(s) (IDS) (filed 08 October 2009) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Withdrawn Objections And/Or Rejections

The rejection to claims 21, 30 and 32 under 35 U.S.C. 112, first paragraph, written description, new matter, for the limitation, "..a point mutant or deletion mutant of erythropoietin which retains stimulation of the production of red blood cells.." (claim 21),

as set forth at pages 5-6 of the previous Office Action (22 May 2009), is *withdrawn* in view of the amendment (08 October 2009). Please see the new rejection below.

The objection to claim 21, as set forth at page 11 of the previous Office Action (22 May 2009), is *withdrawn* in view of the amendment (08 October 2009).

Claim Rejections-35 USC § 112, First Paragraph, Written Description

Claims 21, 30 and 32 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The basis for this rejection is set forth at pages 3-5 of the previous Office Action (22 May 2009).

The instant specification fails to provide adequate written description for EPO with modified N-linked glycosylation patterns, EPO with point mutations and deletion mutants in the helices or interhelical regions of the four alpha helical bundle motif in the context of the instant invention. The instant specification fails to provide adequate written description for Gas6 fragments lacking the A domain, Gas6 consisting essentially of the D domain and Gas6 mutant having at least 95% sequence identity at the amino acid level compared to wildtype Gas6 protein in the context of the instant invention.

Applicant argues that the specification provides adequate written description of the compounds recited in the present claims. Applicant argues that EPO with modified N-linked glycosylation patterns was known in the art at the time of filing. Applicant cites submitted reference US 2003/0077753. Applicant argues that point mutations and deletion mutants in the helices or interhelical regions of the four alpha helical bundle

motif in EPO that stimulate the production of red blood cells were known in the art at the time of filing. Applicant cites submitted references (Bittorf et al., FEBS Lett, 1993 and Boissel et al., J. Biol. Chem, 1993). Applicant argues that no listing of particular Gas6 fragment or mutants need be recited in the claims. Applicant argues that the domains responsible for the ligand activity of Gas6 were well known to the skilled person. Applicant cites submitted reference Manfioletti et al. (Mol Cell Biol, 1993). Applicant discusses the Written Description Training Materials. Applicant argues that the present case is analogous to Example 11B of the Written Description Training Materials.

Applicant's arguments have been fully considered but are not found persuasive. None of the references cited teach EPO with modified N-linked glycosylation patterns and/or EPO point mutations and deletion mutants in the helices or interhelical regions of the four alpha helical bundle motif **which ensure a synergistic rescue effect on erythropoiesis when combined** with Gas6 fragment or mutants. The functional and structural characteristic of EPO mutants and Gas6 mutants in the context of synergistic rescue was ***NOT*** known in the art at the time of filing. In addition, the instant specification fails to teach a structure for wildtype Gas6 protein. The specification states, "..the reference to Gas6 **includes species (human or animal)**.." (page 10, lines 16-28). Thus, the specification teachings include all species of Gas6 protein. The specification does not provide adequate written description for a Gas6 mutant having at least 95% sequence identity at the amino acid level compared to ***any species*** of wildtype Gas6 protein, which can be employed in the context of the instant invention.

Lastly, Example 11B from the Written Description Training Materials is not applicable to the instant case. Example 11B is from an Art-Recognized Structure-Function Correlation. Example 11B teaches that the protein has a novel activity Y. Example 11B teaches that the specification discloses data from deletion studies that identify two domains as critical to activity Y (i.e. a binding domain and a catalytic domain). This is not the instant case. The instant specification teaches novel activity **synergistic rescue effect on erythropoiesis when EPO protein and Gas6 protein are combined. *However*, the instant specification fails to identify domains in EPO and Gas6 which are critical to the novel activity of synergistic rescue effect on erythropoiesis when EPO protein and Gas6 protein are combined.**

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained

Claim Rejections-35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 30 and 32 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for the treatment of anemia in a patient which comprises administering to said patient a combination of **wildtype Gas6 protein (or a physiologically tolerated salt of wildtype Gas6 protein)** and **wildtype erythropoietin (or epoetin or**

darbepoietin or a physiologically tolerated salt of wildtype erythropoietin, epoetin or darbepoietin) simultaneously thereby ensuring a synergistic rescue effect on erythropoiesis in said patient, does not reasonably provide enablement for the claims as currently claimed.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The basis for this rejection is set forth at pages 6-9 of the previous Office Action (22 May 2009).

The specification states that the present invention is based on a first observation that growth arrest-specific gene 6 (Gas6) expression is required for the development of sufficient erythroid reserves and to ensure an adequate hematopoietic response to an anemic challenge in human and/or mammals. The specification states that Gas6 is a new member of the vitamin K-dependent protein family (page 3). The specification teaches that a synergistic effect of increased hematocrit levels was seen, when recombinant Gas6 protein and recombinant EPO protein were administered to Gas6-/- knockout mice treated with PHZ to induce anemia (Figure 4B).

Applicant argues that "modified N-linked glycosylation pattern" is recited in the claims and that such EPO variants were known in the art at the time the application was filed. Applicant cites US 2003/0077753 and argues that the instant application describes N-linked glycosylation variants that are biologically active. Applicant argues that erythropoietin has been limited to point mutations in the helices or interhelical

regions of the four alpha helical bundle motif. Applicant argues that such point mutants and deletion mutants have been shown to display biological activity. Applicant cites Bittorf et al. and Boissel et al. Applicant argues that for such mutants no further testing is required with regard to generating and screening the molecules for activity. Applicant argues that structural information of Gas6 was readily available to the skilled person at the time of filing the application. Applicant cites WO 96/28548 (reference submitted by Applicant). Applicant argues that WO 96/28548 is cited in the instant application. Applicant argues that the specification teaches that the carboxy-terminal globular G domains of Gas6 are responsible for receptor binding, which is validated in WO 96/28548. Applicant cites MPEP 2164.01 and argues that a patent need not teach and preferably omits what is well known in the art. Applicant cites case law.

Applicant's arguments have been fully considered but are not found persuasive. The instant claims are to a method for the treatment of anemia in a patient which comprises administering to said patient ***a combination*** of Gas6 protein and erythropoietin ***thereby ensuring a synergistic rescue effect on erythropoiesis in said patient***. Applicant's citation of MPEP 2164.01 is not applicable because the instant invention is novel. It is not well known in the art. Bittorf et al. and Boissel et al. teach structural/functional characterization of EPO in the context of EPO receptor binding and cell proliferation. Chen et al. (WO 96/28548) teach structural/functional characterization of Gas6 in the context of activating the Rse receptor or Mer receptor and differentiation. **There are no structural and functional teachings of Gas6 mutants and EPO mutants in the context of the instant invention (i.e. synergistic**

rescue effect on erythropoiesis in said patient). The references cited by Applicant fail to teach a specific Gas6 protein lacking the A domain, a specific Gas6 protein consisting essentially of the D domain and/or a Gas6 mutant having at least 95% sequence identity compared to wild type Gas6 protein ***combined*** with specific EPO modified N-linked glycosylation variants, specific point mutation in the helices or interhelical regions of the four alpha helical bundle motif in EPO and/or specific deletion mutant in the helices or interhelical regions of the four alpha helical bundle motif in EPO ***thereby ensuring a synergistic rescue effect on erythropoiesis in said patient.*** Further, the specification states, "..the reference to Gas6 **includes species (human or animal)**.." (page 10, lines 16-28). Thus, the specification teachings include all species of Gas6 protein. The specification fails to teach how to make a Gas6 mutant having at least 95% sequence identity at the amino acid level compared to any species of wildtype Gas6 protein, which can be employed in the context of the instant invention. The instant examples **only** employ recombinant wildtype EPO protein and recombinant wildtype Gas6 protein to demonstrate a synergistic rescue effect on erythropoiesis in mice animal models. There are no working examples in the specification or in the art, which teach Gas6 and EPO polypeptides less than 100% identity and that have a synergistic rescue effect on erythropoiesis.

The instant specification demonstrates synergistic effects of administering Gas6 and EPO ***simultaneously*** in anemic animal models Gas6-/- model (page 28, lines 11-21; Figure 4) and heterozygous EPO deficient model 134.3 LC, EPO-TAg(H) (page 32, lines 8-21; Figure 5). ***However***, the specification fails to demonstrate synergistic effects

of administering Gas6 and EPO ***sequentially*** in said anemic animal models. Further, the specification does not teach the definition of "sequentially". The term "sequentially" could encompass 2 days, 2 minutes or 2 months. There is no evidence that administration of EPO and Gas6 separated by a significant amount of time would lead to a synergistic result.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 30 and 32 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The basis for this rejection is set forth at pages 9-10 of the previous Office Action (22 May 2009).

Claim 21 is indefinite because of the recitation, "..a Gas6 mutant having at least 95% sequence at the amino acid compared to the wildtype Gas6 protein..".

Applicant argues that the term "..said Gas6 fragment.." has been deleted from the claims and has been replaced with "..compared to the wild type Gas6 protein..". Applicant argues that the wildtype Gas6 sequence was known in the art at the time of filing and need not be recited in the claims. Applicant cites the instant specification (page 10, lines 17-20).

Applicant's arguments have been fully considered but are not found persuasive. The specification states, "the reference to Gas6, a mutant, variant or derivative thereof includes the Gas6 protein as encoded by the human Gas6 gene (Maniotti et al.)". "The reference to Gas6 **includes species (human or animal)**.." (page 10, lines 16-28). Thus, the specification teachings include all species of Gas6 protein. The instant claim recites "at least 95% sequence identity" but fails to recite a SEQ ID NO:. The recitation of sequence percent identity at the amino acid level in the absence of a referenced SEQ ID NO: renders the claim indefinite. The metes and bounds of claim cannot be determined because the claim fails to recite a structure (i.e. SEQ ID NO:) to discern at least 95% identity.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

NEW CLAIM REJECTIONS/OBJECTIONS

Claim Rejections-35 USC § 112, First Paragraph, Written Description (New Matter)

Claims 21, 30 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The specification as originally filed does not provide support for the invention as now claimed in claim 21:

"..erythropoietin having a modified N-linked glycosylation pattern.."

"..erythropoietin with a point mutation in the helices or interhelical regions of the four alpha helical bundle motif, wherein said erythropoietin with a point mutation stimulates the production of red blood cells.."

"..a deletion mutant of erythropoietin in the helices or interhelical regions of the four alpha helical bundle motif, wherein said deletion mutant of erythropoietin stimulates the production of red blood cells.."

Applicant's amendment, filed 08 October 2009, asserts that no new matter has been added and directs support to page 12, lines 24-27 and page 13, lines 3-4, for the written description for the above-mentioned "limitations". Applicant argues that the passage clearly provides basis for "deletion mutants of erythropoietin" as well as for "erythropoietin with a point mutation". Applicant argues that for reasons of clarity, they have opted to state in the claim what is intended with biological activity of EPO (stimulation of the production of red blood cells).

The Examiner has found the following teachings:

Erythropoietin or EPO as used herein refers to the naturally occurring human cytokine, produced primarily in kidneys, which stimulates the production of red blood cells, as well as analogues, mutants, variants, or derivatives thereof, or a physiologically tolerated salt of said EPO derivative. Well described erythropoietin analogues are the hyperglycosylated recombinant proteins epoetin and darbepoietin or NESP, of which the structures differ from naturally occurring EPO only by the number of N-linked oligosaccharides on the protein (page 12, lines 14-21).

The invention however, also envisages the possible development of other activators of the EPO receptor, which if developed into EPO analogues, can be used in the context of the present invention. The expression product of deletion mutants of a synthetic human Epo cDNA, wherein the point mutations and small deletions in helices and interhelical regions of the four alpha helical bundle motif have been show to display biological activity (Bittorf et al. (1993) FEBS Left 336, 133-136;Boissel et al. (1993) J. Biol. Chem. 268, 15983-15993) (page 12, lines 21-28). US patent application 2003/0077753 describes EPO variants with modified glycosylation pattern (page 13, lines 1-4).

Applicant arguments have been fully considered but are not found persuasive. The citation of Bittorf et al., Boissel et al. J. Biol. Chem and US patent application 2003/0077753 in the instant specification is not contemplation of the instant method as currently claimed. The instant specification does not contemplate **specific** EPO analogues, EPO mutants, EPO variants, or EPO derivatives. The instant specification does not state, "as used herein EPO analogues, EPO mutants, EPO variants, or EPO derivatives refer to...". Further, the reference to US patent application 2003/0077753 does not indicate an intended incorporation by reference. Mere reference to another application, patent, or publication is not an incorporation of anything therein into the application containing such reference for the purpose of the disclosure required by 35 U.S.C. 112, first paragraph. *In re de Seversky, 474 F.2d 671, 177 USPQ 144 (CCPA 1973).*

At least for example, pages 12-13 discuss hyperglycosylation and not any any change in the glycosylation pattern (which would include deletion of glycosylation sites) embraced by the claims. Pages 12-13 discuss the particular point mutations of Boissel and Bittorf to human EPO and not any or all mutations that could be made in these regions. To the degree the claims embrace embodiments not specifically disclosed or contemplated, the claims contain new matter.

The instant methods, as currently recited, were not contemplated in the disclosure at the time of filing. The instant claims now recite limitations, which were not disclosed in the specification as filed and now change the scope of the original disclosure. Applicant is required to cancel the new matter in the response to this Office action. Alternatively, Applicant is invited to provide specific written support for the "limitations" indicated above or rely upon the limitations set forth in the specification as filed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21, 30 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. US 6,169,070 B1.

Chen et al. teach that Gas6 may be used to enhance re-population of mature blood cell lineages in patients. Chen et al. teach that it is contemplated that Gas6 will act via an enhancement of the proliferation and/or differentiation of hematopoietic cells. Chen et al. teach that Gas6 may be used for treating diseases characterized by a decrease in blood cells such as anemia, aplastic anemia and the repair of kidney tissue (column 32, lines 46-63). Chen et al. teach that for use in hematopoiesis, Gas6 may be administered with erythropoietin (column 33, line 59-column 34, line 8).

Absent evidence to the contrary, Chen et al. meet the limitations of the instant claims and the synergistic results would be inherent to the method of Chen et al. The claims do not require any particular amounts to be administered or any particular timing or order of administration. Evidence that the method of Chen et al. does not result in a synergistic effect will be viewed as evidence supporting the examiner's contention that the scope of the claims is not enabled.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
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11/18/09